

Original Article**Prevalence of Musculoskeletal Manifestations among Primary Hypothyroid Patient in North India**

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Mobile: +9568187137, Email: docapg@gmail.com**Abstract****Objective:** To study the prevalence of musculoskeletal manifestations among the primary hypothyroid patients of North India.**Method:** 200 primary hypothyroid patients of age group 20-80 years were selected from Rheumatology clinic, S.N. Medical College and Hospital, Agra during the period of one year August 2016 to August 2017, a detailed clinical history and physical examination was done. Various investigations and diagnostic criteria were used during study.**Result:** 83% (166) were female and 17% (34) were male. The mean age of the respondents (n=200) was 52.35 ± 12.36 years. Mean body weight was 69.21 ± 11.896 . Mean duration of drug intake 2.818 years. Prevalence of osteoarthritis in this study came out to be maximum (55%) followed by RA (24%) then SLE (12.5%), Fibromyalgia (2.5%), ankylosing spondylitis (2%), MCTD(1.5%), systemic sclerosis and Sjogren's syndrome observed in 1% study population, other musculoskeletal manifestations were Myalgia (71.5%), Stiffness and Muscle cramp (80%), Arthralgia (60%), Adhesive capsulitis (25%), Carpel tunnel syndrome (8%), Trigger finger (7%), Tarsal tunnel syndrome (2%), Dupuytren's contracture (5%), non inflammatory back pain (30%)**Conclusion:** Various musculoskeletal manifestations are commonly associated with hypothyroidism. Osteoarthritis being most common followed by rheumatoid arthritis. Early detection of hypothyroidism in patients suffering from rheumatic disease and vice versa and its prompt treatment can improve the clinical outcome of disease.**Keywords:** Primary Hypothyroidism, Musculoskeletal, Osteoarthritis, Rheumatic diseases.

Introduction

The thyroid gland produces two related hormones, thyroxin (T4) and triiodothyronine (T3). Acting through thyroid hormone receptors α and β , these hormones play a critical role in cell differentiation during development and help maintain thermogenic and metabolic homeostasis in the adult. Autoimmune disorders of the thyroid gland can stimulate overproduction of thyroid hormones (thyrotoxicosis) or cause glandular destruction and hormone deficiency (hypothyroidism)^[1]. Primary hypothyroidism is due to disease in the thyroid; thyroid-stimulating hormone (TSH) is increased. The most common cause is autoimmune. Primary hypothyroidism is due to disease in the thyroid; thyroid-stimulating hormone (TSH) is increased. The most common cause is autoimmune. It usually results from Hashimoto thyroiditis and is often associated with a firm goiter or, later in the disease process, with a shrunken fibrotic thyroid with little or no function.^[2]

Primary hypothyroidism is an endocrine disorder which affects many organs of which musculoskeletal involvement is one of the important disease manifestations. Cause of overlap between hypothyroidism and rheumatic diseases could be probably because of autoantibodies. At the molecular level probable mechanism is auto-reactive T cells which recognize auto antigens expressed on thyroid tissue and other organs. Among rheumatic diseases most commonly encountered ones are Osteoarthritis, Rheumatoid arthritis, SLE, Fibromyalgia, Ankylosing spondylitis, MCTD, Systemic sclerosis and Sjogren's syndrome, musculoskeletal manifestations includes myalgia, stiffness and muscle cramp, Arthralgia, Adhesive capsulitis, carpal tunnel syndrome, Trigger finger, Tarsal tunnel syndrome, Dupuytren's contracture, Back pain (non inflammatory). Myopathy due to hypothyroidism causes stiffness and aching of muscles and is worsened by cold temperatures. Muscle mass may be reduced or enlarged due to interstitial myxedema. Muscle mass may be

slightly increased, and the muscles tend to be firm.

Materials and Methods

This was a hospital based cross sectional study. Patients of both sexes attending Rheumatology and Endocrinology outdoor, between 20 and 80 years of age of Primary Hypothyroidism were included. A total of 200 patients were taken for study after given their informed consent. Patients suffering from severe comorbid illness like – diabetes, alcoholic, HIV infection, preexisting neuro muscular disorder, prolonged drug intake like fibrate, statin, corticosteroid were excluded from study.

An inclusion criterion includes patients suffering from Primary hypothyroidism. Exclusion criteria includes patients who are not willing to participate in this study, patients suffering from severe comorbid illness like – diabetes, alcoholic, HIV infection, preexisting neuro muscular disorder, prolonged drug intake like Fibrate, Statin, corticosteroid.

Hematological investigations included - TSH, FT3, FT4, anti thyroid peroxidase (Anti TPO)

Special investigation include Anti CCP, RA Factor, Anti smith, Anti RO, Anti LA, HLAB27, ANA, anti SCL70, Anti-centromere antibody, synovial fluid examination.

Radiological investigations done were - X-ray and Ultrasonography of concerned joint, Magnetic resonance imaging of concerned joint if required.

Result

In this study the male to female ratio was 1:5, The mean age of the respondents (n=200) was 52.35 ± 12.36 years, mean body weight was 69.21 ± 11.896 . Prevalence of Rheumatological disorder were – osteoarthritis in our study performed with 200 primary hypothyroid patient came out to be maximum 55% Rheumatoid arthritis 24%, SLE 12.5%, Fibromyalgia 2.5%, ankylosing spondylitis 2%, Mixed connective tissue disorder (MCTD) 1.5%, systemic sclerosis and Sjogren's syndrome observed in 1% study population (table-

1). Various other musculoskeletal manifestation were myalgia 71.5%, stiffness and muscle cramp-80%, Arthralgia-60%, Adhesive capsulitis -25%, carpal tunnel syndrome-8%, Trigger finger-7%, Tarsal tunnel syndrome 2%, Dupuytren's

contracture-5% Back pain (non inflammatory)-30 (table-2), Prevalence of various musculoskeletal manifestation increases with period of hypothyroidism (table -3)

Table 1 Common table showing age wise distribution, sex wise prevalence and total prevalence of different rheumatological manifestation of hypothyroidism

Age Group	Total No. of Case	RA		OA		SLE		Fibromyalgia		Systemic Sclerosis		Sjogren's Syndrome		Ankylosing Spondylitis		MCTD	
		M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
< 30	9	-	1	-	-	1	6	-	-	-	-	-	-	1	-	-	-
31 – 40	26	1	1	-	2	-	11	-	3	1	1	-	1	2	1	1	1
41 – 50	42	6	17	5	5	-	5	-	2	-	-	-	1	-	-	-	1
51 – 60	73	4	15	6	46	-	2	-	-	-	-	-	-	-	-	-	-
61 – 70	40	1	3	3	33	-	-	-	-	-	-	-	-	-	-	-	-
> 70	10	-	-	2	8	-	-	-	-	-	-	-	-	-	-	-	-
Total	200	12	37	16	94	1	24	-	5	1	1	-	2	3	1	1	2
Sexwise Prevalence		24.49	75.51	14.55	85.45	4	96	0	100	50	50	0	100	75	25	33.33	66.67
G. Total		49		110		25		5		2		2		4		3	
G. Prevalence		24.5		55		12.5		2.5		1		1		2		1.5	

Table 2- Prevalence of Other Musculoskeletal Disorder in Study Population (combination's of disorder were present)

Disease	Age (in Years)						
	< 30	31- 40	41 – 50	51 – 60	61 – 70	> 70	Total
Myalgia	3	43	66	24	5	2	143
Stiffness & Muscle Cramp	9	31	78	32	7	3	160
Arthralgia	2	18	24	46	21	9	120
Adhesive Capsulitis	-	-	4	9	16	21	50
Carpel Tunnel Syndrome	-	4	7	5	-	-	16
Trigger Finger	-	2	9	2	1	-	14
Dupuytren's Contracture	-	-	3	4	2	1	10
Tarsal Tunnel Syndrome	-	-	1	2	1	-	4
Back Pain (Non-inflammatory)	-	17	21	12	-	-	60

Table 3- Duration of Drug Intake and occurrence of musculoskeletal manifestations

Diseases	Duration of Drug Intake (in Years)			
	< 5	6 – 10	> 10	Total
RA	17	27	5	49
OA	23	74	13	110
SLE	5	20	0	25
Systemic sclerosis	0	1	1	2
Sjogrens syndrome	0	2	0	2
MCTD	0	2	1	3
Fibromyalgia	0	5	0	5
Ankylosing spondylitis	1	3	0	4
Total	46	134	20	200
Prevalence	23	67	10	100

Discussion

Thyroid gland Disorders often present with musculoskeletal signs and symptoms. Probably due to common pathophysiology, that is Autoimmune nature of most of the

rheumatological and thyroid disease, The relationship between thyroid disorders and rheumatic diseases is significant and occurs in various combinations, HLA-DR polymorphism are the best documented genetic risk factors for

autoimmune hypothyroidism especially HLA-DR3, -DR4, and -DR5 in Caucasians. A weak association also exists between polymorphisms in *CTLA-4*, T cell-regulatory gene, and autoimmune hypothyroidism. Both of these genetic associations are shared by other autoimmune diseases which may explain the relationship between autoimmune hypothyroidism and other autoimmune diseases^[3]. Genetic factors also contribute to the occurrence of RA. The alleles known to confer the greatest risk of RA are located within the major histocompatibility complex (MHC). It has been estimated that one-third of the genetic risk for RA resides within this locus. Most, but probably not all, of this risk is associated with allelic variation in the HLA-DRB1 gene, which encodes the MHC II β -chain molecule^[4] thus common genetic predisposition between AITD and RA could be one of the reason for there co existence in many patients. In this study prevalence of rheumatoid arthritis among 200 hypothyroid patient was found to be 24.5% including 18.5% of females and 6% males which is supported by study conducted by other authors too^[5,6]

Osteoarthritis (OA) isn't caused by immune system issues. Emerging evidence has identified genetic mutations that confer a high risk of OA, the best replicated is a polymorphism within the growth differentiation factor 5 gene. This polymorphism diminishes the quantity of GDF5; GDF5 has its main influence on joint shape, and genes predisposing to OA are likely to increase risk of disease based on their effects on joint development and shape^[7], although pathogenesis of both AITD and OA are different but there co existence in patients are quite common. Prevalence of osteoarthritis in study population is 55% and highest prevalence is in 51-60 yrs age group i.e. 71.23%. Prevalence in female is 47% as compared to male 8%. supported by previous study by Alakes Kumar Kole, Rammohan Roy, Dalia Chanda Kole^[8]

Older women are at high risk of OA in all joints, a risk that emerges as women reach their sixth

decade. In this study out of 94 hypothyroid females having osteoarthritis, 56 were in the age group between 51-60 years that is in 6th decade which depicts, that as the women reach near menopausal age prevalence of osteoarthritis increases, this is probably due to decline in oestrogen levels after menopause. BMI is also positive contributory factor for the development of Osteoarthritis which is also proved by this study, having max 54 patients with BMI ranging in overweight category (BMI 25-29.9 Kg/m²) out of total 110 osteoarthritis individuals.

Systemic lupus erythematosus (SLE) is an autoimmune disease in which organs and cells undergo damage initially mediated by tissue-binding autoantibodies and immune complexes. In most patients, autoantibodies are present for a few years before the first clinical symptom appears. Ninety percent of patients are women of child-bearing years; people of all genders, ages, and ethnic groups are susceptible^[9] In this study 25 out of 200 hypothyroid patients had Systemic lupus erythematosus, 24 were females and 1 was male. Prevalence of SLE in study population was 12.5% and highest prevalence was seen in age group 20-30 years (77.78%). Prevalence in female was 12% as compared to male 1%, which is well in coherence with other studies conducted in past^[10] Serological overlap among SLE, and AITD exists^[11-14] that might be the reason for their association.

Patients with fibromyalgia have reduced pain tolerance to stimuli that are normally not painful such as pressure, heat, and electric pulse, at the classic tender points and control points (allodynia). They also perceive pain as being more intense and extending for a longer time (hyperalgesia). This abnormal sensory pain processing could be explained by increased pain facilitation and reduced pain-inhibiting mechanisms on the spinal and cerebral levels. Fibromyalgia patients also displayed abnormal temporal summation of pain after a series of thermal stimulations, called "wind-up." The concentration of substance P, a neuromodulator of

pain, in the cerebrospinal fluid was threefold greater in fibromyalgia patients than in controls^[15]. Thyroid hormone regulates substance P in discrete nuclei of the brain, in the anterior pituitary, in the lumbar spinal cord, and in the dorsal root ganglia. Most significantly, however, thyroid hormone directly regulates transcription of the preprotachykinin gene, which codes for preprotachykinin-A (the precursor of substance P) and the substance P receptor. Studies confirm the negative regulation of substance P by thyroid hormone: increasing the availability of thyroid hormone decreases levels of substance P; decreasing thyroid hormone increases levels of substance P^[16], that might be the possible reason for association between fibromyalgia and hypothyroidism, its prevalence in this study was 2.5%. All were females

SSc shows modest heritability, and the genetic associations identified to date make only a small contribution to disease susceptibility. concordance for antinuclear antibody (ANA) positivity is significantly higher. The risk of Raynaud's phenomenon, interstitial lung disease, and other autoimmune diseases, including systemic lupus erythematosus (SLE) rheumatoid arthritis and autoimmune thyroiditis^[17]. Its prevalence in study population was 1%, equal prevalence in both male and female (0.5%).

Sjögren's syndrome is characterized by both lymphocytic infiltration of the exocrine glands and B lymphocyte hyperreactivity. An oligomonoclonal B cell process, which is characterized by cryoprecipitable monoclonal immunoglobulins (IgMκ) with rheumatoid factor activity, is evident in up to 25% of patients.^[18] Prevalence of Sjögren's syndrome in study population was 1%. Jara L.J. et.al.^[19] in their study found that, The coexistence of SS and thyroiditis is frequent and suggests a common genetic or environmental factor predisposition with similar pathogenic mechanisms. primary Sjögren's syndrome (pSS) was ten times more frequent in patients with autoimmune thyroid

disease and autoimmune thyroiditis was nine times more frequent in pSS

ANKYLOSING SPONDYLITIS is an inflammatory disorder of unknown etiology that primarily affects the axial skeleton; peripheral joints and extra-articular structures are also frequently involved. In this study 4 out of 200 had ankylosing spondylitis. 3 patients were male and 1 was female, Prevalence of ankylosing spondylitis in study population is 2%, Prevalence in female is 0.5% as compared to male 1.5%.

MCTD prevalence in this study was 1.5%, Prevalence in female was 1% as compared to male 0.5 %. Alkes koel⁽⁸⁾ in their study found prevalence of MCTD 1.67% which is close to prevalence we concluded in this study,

Arthropathy in hypothyroidism is Non-inflammatory arthralgia, stiffness and arthritis. Arthritis is non-inflammatory, highly viscous joint effusions primarily affecting the knees, wrists and hands. The symptoms may mimic rheumatoid arthritis. Arthropathy can be treated with thyroid hormone replacement therapy. Adhesive capsulitis, also known as frozen shoulder, is a regional skeletal problem reported in association with thyroid disorders. In this study prevalence of myalgia was 71.5%, stiffness and muscle cramp-80%, Arthralgia-60%, Adhesive capsulitis-25%, carpal tunnel syndrome -8%, Trigger finger -7%, Tarsal tunnel syndrome-2%, Dupuytren's contracture -5% Back pain (non inflammatory) -30%.

Conclusion

Various musculoskeletal manifestations are commonly associated with hypothyroidism.

1. Among various musculoskeletal manifestations, most common is osteoarthritis followed by rheumatoid arthritis.
2. These musculoskeletal manifestations increase with the increasing in duration of hypothyroidism which can be indirectly correlated with the duration of drug intake.

3. These MSK manifestations are more common in female hypothyroid patients as compared to male hypothyroid patients
4. The prevalence of osteoarthritis increases as women reach menopausal age
5. Development of MSK disorders, such as Osteoarthritis is commonly associated with increased BMI.
6. Association of primary hypothyroidism with major rheumatic manifestations was as follows:
 - a) Osteoarthritis -55% (maximum)
 - b) RA -24%
 - c) SLE -12.5%
 - d) Fibromyalgia -2.5% ,
 - e) Ankylosing spondylitis -2%,
 - f) MCTD- 1.5%,
 - g) Systemic sclerosis -1%
 - h) Sjogren's syndrome 1%.

The study emphasizes the role of thyroid status (hypothyroidism) in patients suffering from various rheumatic diseases. Early detection of hypothyroidism and its prompt treatment with thyroid replacement therapy can result into dramatic changes in alleviating the symptoms of disease and outcome.

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References

1. Disorder of thyroid gland. J. Larry Jameson, Susan J. Mandel, Anthony P. Weetman. Harrison 19th edition page no 2283
2. Hypothyroidism (Myxedema) By Jerome M. Hershman, MD, MS, Distinguished Professor of Medicine Emeritus; Director of the Endocrine Clinic, David Geffen School of Medicine at UCLA; West Los Angeles VA Medical Center
3. J. Larry Jameson, Susan J. Mandel, Anthony P. Weetman Disorders of the Thyroid Gland Disorders of the Thyroid Gland chapter 405 page 2290
4. Ankoor Shah, E. William St. Clair Rheumatoid Arthritis HARRISON'S principle of internal medicine page no2139
5. Joshi P, Agarwal A, Vyas S, Kumar R. Prevalence of hypothyroidism in rheumatoid arthritis and its correlation with disease activity. Trop Doct. 2017 Jan;47(1):6-10. Epub 2016 Jan 20
6. Enas A. Elattara, Takwa B. Younesa, Sameh A. Mobasherb Hypothyroidism in patients with rheumatoid arthritis and its relation to disease activity. <http://www.err.eg.net> on Sunday, November 26, 2017, IP: 106.79.62.217]
7. David T. Felson Osteoarthritis Immune-Mediated, Inflammatory, and Rheumatologic Disorders chapter 394 page 2226
8. Alakes Kumar Kole et al. Rheumatic manifestations in primary hypothyroidism. Indian Journal of Rheumatology 8 (2013) 8, 13.
9. Bevera Hannahs Hahn, Systemic Lupus Erythematosus, page 2127 Harrison 19th edition
10. Abdulla Watadab Naim Mahroumab Hypothyroidism among SLE patients: Case-control study Autoimmunity Reviews 2016; 15(5): 484-486.
11. Hijmans W, Doniach D, Roitt IM, Holborow EJ. Serological overlap between lupus erythematosus, rheumatoid arthritis, and thyroid auto-immune disease. Br Med J (1961) 2:909–14.10.1136/bmj.2.5257.909
12. Halberg P, Bertram U, Soborg M, Nerup J. Organ antibodies in disseminated lupus erythematosus. Acta Med Scand (1965) 178:291–9.10.1111/j.0954-6820.1965.tb04273.
13. Jonsson H, Nived O, Sturfelt G. Thyroid disorders in systemic lupus erythematosus are associated with secondary Sjögren's

- syndrome. Ann Rheum Dis (1987) 46:349.10.1136/ard.46.4.349
14. Sakata S, Nakamura S, Nagai K, Komaki T, Kawade M, Niwa T, et al. Two cases of systemic lupus erythematosus associated with hyperthyroidism. Jpn J Med (1987) 26:373–6.10.2169/internalmedicine1962.26.373
 15. Frederick wolfe • johannes j. rasker fibromyalgia chapter 52 kelly rheumatology 9th edition
 16. jackie Yellin BA Journal Rice University Clinical Bulletin of Myofascial Therapy Volume 2, 1996 - Issue 2-3 Pages 23-30 | Published online: 15 Oct 2008
 17. John Varga Systemic Sclerosis (Scleroderma) and Related Disorders chapter382 page 2155
 18. Haralampos M. Moutsopoulos, Athanasios G. Tzioufas Sjogren's Syndrome harrison 19th edition chapter 383 page 2166
 19. Jara LJ, Navarro C, Brito-Zeron Mdel P, Garcia-Carrasco M, Escárcega RO, Ramos-Casals M. Thyroid disease In Sjögren's syndrome. Clin Rheumatol. 2007 Oct;26(10):1601-6.